Etiologic Classification Criteria of ARCO on Femoral Head Osteonecrosis, Part 2: Alcohol-Associated Osteonecrosis

Abstract

Objective: Although alcohol is a leading risk factor for osteonecrosis of the femoral head (ONFH) and its prevalence reportedly ranges from 20% to 45%, there are no unified classification criteria for this sub-population. In 2015, Association Research Circulation Osseous (ARCO) decided to develop classification criteria for alcohol-associated ONFH (AA-ONFH).

Methods: In June of 2017, ARCO formed a task force to conduct a Delphi survey. The task force invited twenty-eight experts in osteonecrosis/bone circulation from eight countries. Each round of the Delphi survey included questionnaires, analysis of replies, and feedback reports to the panel. After three rounds of the survey, consensus was reached on the classification criteria. The response rates for the three Delphi rounds were 100% (Round 1), 96% (Round 2), and 100% (Round 3).

Results: The consensus on the classification criteria of AA-ONFH included: 1) patients should have a history of alcohol intake > 400 mL/week (320 g/week, any type of alcoholic beverage) of pure ethanol for more than 6 months; 2) ONFH should be diagnosed within 1 year after alcohol intake of this dose; and 3) patients should not have other risk factor(s).

Conclusion: ARCO established classification criteria to standardize clinical studies concerning AA-ONFH.

Key words: osteonecrosis; avascular necrosis; hip; femoral head; alcohol; Delphi

Introduction

Since 1922, when the association between osteonecrosis of the femoral head (ONFH) and alcohol abuse was first presented,[1] alcohol consumption has been known as an important risk factor for non-traumatic osteonecrosis of the femoral head (ONFH). [2-4] Epidemiologic studies previously reported that 20% to 45% of ONFH patients were associated with alcohol overuse.[5-10] However, individual susceptibility for the development of alcohol-associated ONFH (AA-ONFH) varies widely and depends not only on the extent of exposure to ethanol, but also to genetic predispositions[11-14] although a statistical significant dose-response relationship was shown in a recent meta-analysis.[15] HIrota et al. reported that, when compared to non-drinker, the odds ratio tended to be increased even in low-risk drinkers; 2.8 [95% confidence interval (CI), 1.0-7.8] in subjects with weekly ethanol intake < 320 g or 2.2 [95% CI, 0.7-6.9] in subjects with < 3200 (g/week per year).[16] On the contrary, the incidence of osteonecrosis was reported to be only 0.3 to 5% in patients with chronic alcoholism. Therefore, it is difficult to practically determine a unifying cut-off dose of alcohol to develop AA-ONFH.[17, 18]

On this context, the definition or classification criteria varies widely across previous studies on AA-ONFH. Among 18 English-written studies published from 2015 to 2017 with a sample size of 200 or more, 6 studies used 400 mL/week as the cut-off level of alcohol exposure,[19-24] 2 studies did 900 mL/week,[25, 26] and one study did 40 g/day for men or 20 g/day for women to defined AA-ONFH.[3] Even a worse problem is that 50% (9/18) did not describe their definition for AA-ONFH.[4, 9, 10, 24, 27-31] Such heterogeneity is an important obstacle for collaborative efforts to study AA-ONFH and makes it difficult to compare the results across the studies or to collect data enough to augment our understanding of AA-ONFH.

In April 2015, Association Research Circulation Osseous (ARCO) addressed some of these issues on classification criteria of non-traumatic ONFH and formed a task force to establishing the criteria for AA-ONFH and glucocorticoid-associated osteonecrosis (GA-ONFH), and conducted a Delphi survey to establish classification issues.

The criteria of GA-ONFH were described elsewhere as a Part 1 study,[blinded by authors] and this is the Part 2 study concerning the criteria for AA-ONFH.

Methods

Participants

The ARCO task force was set up to prepare the Delphi survey and consisted of 7 members; 4 orthopaedic surgeons, 1 expert researcher on bone circulation/osteonecrosis, 1 rheumatologist and 1 statistician/methodologist. The task force performed a search of PubMed, using the key search terms "osteonecrosis", "avascular necrosis", "aseptic necrosis", and "alcohol" for entries from January 1, 1960, to May 31, 2017. A total of 50 reports on AA-ONFH were identified and reviewed. The task force selected 6 key studies which investigated the risk of ONFH and alcohol intake including cross-sectional, case-control and cohort studies (Supplementary 1). Through the comprehensive literature review, the task force raised 4 issues to develop novel etiologic classification criteria of AA-ONFH; 1) whether panelists necessitated classification criteria for AA-ONFH; 2) the minimal dose of alcohol intake; 3) the latent period after alcohol intake of such dose, when a diagnosis of ONFH should be made; and 4) how to classify ONFH patients who have other risk factor(s) than alcohol.

In June of 2017, the task force initially invited 30 experts and ARCO made the panel qualifications for the Delphi study; college faculty, more than 10 years of clinical and/or research experience, and 3 or more publications on bone circulation/osteonecrosis. Among the 30 experts, one declined the invitation and one did not reply to the invitation. The remaining 28 experts on osteonecrosis/bone circulation participated in the Delphi procedure. The panel members had a mean of approximately 18 years of clinical and/or research experience.

The modified Delphi procedure

The modified Delphi technique is a means of reaching a group consensus through multiple rounds of anonymous feedback and iterations and, especially, is valuable in situations where imprecise or contradictory opinions exist.[32] The details of our Delphi method are referred to the Part 1: glucocorticoid-associated osteonecrosis. Briefly, in the first round, the panel members were asked to answer 4 open-ended questions on the above-mentioned issues. In the second and further rounds, the panel members were asked to answer the revised questionnaires on the issues, on which consensus was not reached in the previous round. Between survey rounds, the response summary of the previous round was presented as anonymous feedback. In our study, 3 rounds were employed until final consensus was obtained on the 4 issues of AA-ONFH. A consensus was determined based on a content validity ratio

(CVR) of 0.357 or greater which means that 19 is a minimum number required to reach a consensus in each questionnaire among 28 panels.[33]

Source of Funding

No external funding was received in support of this work and ARCO.

Results

Through three consecutive Delphi rounds, full consensus was reached on the classification criteria of AA-ONFH.

Round 1: Open round

Four questionnaires were sent to the panel members, and the response rate was 100% in Round 1.

From the replies to the first Delphi survey, consensus was reached on one issue (question 1) about the necessity for the classification criteria. Twenty-three panel members (82.1%) agreed with the necessity for the classification criteria, whereas five members (17.9%) disagreed. The most common reason for the agreement was that although alcohol is a leading risk factor of non-traumatic ONFH, there are no defined classification criteria.

Consensus was not reached on the remaining four issues; minimal dose of alcohol consumption, duration of alcohol consumption, latent period, as well as how to classify patients with multiple risk factors (Table 1). Several panel members also suggested changing the term “alcohol-induced” to “alcohol -associated” because the exact causal relationship between alcohol intake and the development of ONFH has yet to be determined.

Round 2: Selecting and limiting round with multiple choice questions

Questionnaires on the three issues, on which consensus was not reached in Round 1, were modified to multiple-choice questions in order to attempt convergence of the various replies. Five multiple-choice questionnaires were made using lists of categories and panelists were asked to select the most appropriate category. The issue of terminology change from “alcohol-induced” to “alcohol-associated” was also included in Round 2.

The response rate was 96% in Round 2**.** Consensus was reached on three issues: the minimum dose of

alcohol consumption; classification of patients with multiple risk factors; and the term issue. However, consensus was not reached on the two issues of the duration of alcohol consumption and the latent period (Table 2).

Round 3: Ranking round

To attempt convergence on the two issues unresolved in Round 2, the panel members were given the opportunity to state whether or not they agreed with the category showing the highest response frequency in Round 2 and to re-enter their rationale or reason why they did not agree. This was to ensure that the respondents had the opportunity to state whether or not they agreed with the category showing the highest response frequency in Round 2. The response rate was 100% in Round 3**.** As consensus was reached on the remaining two queries, the classification criteria for AA-ONFH was made (Table 3).

Final consensus

To classify an ONFH patient as an AA-ONFH patient: 1) they should have a history of mean alcohol consumption > 400 mL/week (320 g/week, any type of alcoholic beverage) for more than 6 months; 2) ONFHs should be diagnosed within one year after alcohol intake of such dose; and 3) the patient should not have other risk factor(s) than excessive alcohol intake (Table 4).

Approval of the consensus

The final consensus on the classification criteria of AA-ONFH was approved in the general meeting of ARCO, which was held in October 25, 2017 in Berlin

Discussion

In 1988, the influence of alcohol on the development of ONFH was first reported in a multicenter case-control study.[34] However, although previous studies showed that current consumption and cumulative amount were positively associated with non-traumatic ONFH, many researchers have used their own criteria for classification or definition. The proportion of AA-ONFH has been variously reported in studies of non-traumatic ONFH. In a systematic review of 67 reports on total hip arthropathy (including 14 Asian studies), 19% had excessive alcohol consumption as an etiologic factor among in 2,593 patients with ONFH.[35] However, in some epidemiological studies with large sample size (N > 150) published during the recent 20 years, the prevalence of AA-ONFH was from 20% to 45%; 36.7% in USA[5], 32.4%

in Korea 31.8%[7], in China[9], 45.2% in Taiwan[10], 31% in Japan[8], and 20.1% in India.[36] Moreover, the frequencies of AA-ONFH in clinical studies having small sample size much more varied across the studies (from 5% to 81%).[37] Such differences can be attributed to ethnicity or regional variation, inclusion and exclusion criteria, and no universal definition of AA-ONFH. Concerning the definition of AA-ONFH, although about 100 years have passed since the discovery of the association between alcohol abuse and ONFH, many recent studies did not pre-define the etiologic classification criteria of AA-ONFH.[4, 9, 10, 28-31, 38] Also, two thirds of our panelists did not answer their own criteria (Table 2).

The Delphi method is used as a consensus-building tool and was useful to deal with a such controversial issue.[39] Through the modified Delphi process, the panel determined the classification criteria for AA-ONFH in the current study. This ARCO criteria requires determination of the dose of alcohol exposure before the classification of AA-ONFH. At-risk drinking is defined as >14 drinks/week for men or >7 drinks/week for women by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).[40] Also, the World Health Organization (WHO) defines hazardous drinking as a regular average consumption of >40 to 60 grams/day for men or >20 to 40 grams/day for women.[41] Since 1 standard drink contains approximately 10 to 14 grams of pure ethanol, the amount at risk is estimated to be about 140 to 420 grams/week for men or 70 to 280 grams/week for women according to the definitions of NIAAA or WHO. Concerning AA-ONFH, previous studies defined alcohol overuse as consumption of pure alcohol >400 mL/week[42] or >400 mL/week for at least 6 months.[43] Since 1 mL of alcohol weighs 0.816 g and the amount of 400 mL pure alcohol is 326.4 g, the amount of pure ethanol (320 grams/week) in the current classification criteria is compatible or higher than in the NIAAA or WHO definition. Additionally, a recent meta-analysis showed that the odds ratio for AA-ONFH was 6.5 in case of average intake of alcohol 400 g/week.[44] Considering above findings, average drinking of pure ethanol 400 mL/week or more can be a risk factor for the development of AA-ONFH in both genders. The cut-off for the risk dose of pure alcohol is expressed as 400 mL/week using this criteria for convenience' sake.

However, it is not easy to get the information about alcohol intake in all patients and the estimates of alcohol consumption could be biased due to limited human memory, a large time variation in drinking, diverse ethanol content and various categories of drink. The assessment methods for alcohol intake include the 7-day recall method, quantity frequency, and graduated quantity frequency.[45] Although the

7-day recall method, where patients report the quantity of alcohol intake on each day of the previous week, is widely used in epidemiological surveys,[46] it is beyond the scope of this study what is the most appropriate assessment tool to use our classification criteria for AA-ONFH. The dose of ethanol in a drink can be determined after obtaining information about its volume and ethanol concentration. Although ethanol conversion factors differ by country, alcohol contents are generally applied: for beer and light-wine 5.0%, for wine 12%, and for spirits 40%. And the amount of pure alcohol (gm) is calculated to be Volume (mL) x Vol-% x 0.816 (g/ml) [47] For example, if he/she drinks 5 bottles (330 mL) of beer, ethanol consumption content is calculated as 330 mL/bottle × 5 bottles × 5% = 82.5 mL and ethanol amount is as 330 mL/bottle × 5 bottles × 5% × 0.816 g/mL = 67.32 gm.

Drinking patterns as well as drinking amount can affect the development of AA-ONFH; regular drinkers were significantly associated with increased risk of AA-ONFH than occasional drinkers.[44, 48, 49] However, to date, no study has determined the risk period for ONFH development after beginning alcohol intake. It can be an issue of discrimination between AA-ONFH and other types of ONFH including idiopathic ONFH. In the current classification criteria, the panel included a minimal duration of alcohol exposure as a criterion (> 6 months).

The natural history of ONFH has been well investigated. More than half of AA-ONFH patients have symptoms several months to years after development of the disease. Thus there is a time lag between the ONFH development and the diagnosis of the disease.[50] The diagnosis is often delayed because the diagnostic work-up is made only after the patient has pain andan MRI is not always used for the diagnosis.[51] unfortunately, we do not have any data on how long the effect of alcohol remains. Thus, it is reasonable to include a certain period from the alcohol intake to the time of diagnosis in the criteria. When non-traumatic ONFH is diagnosed 1 year after abstinence from drinking, according to the ARCO criteria, he/she cannot be classified as AA-ONFH.

Other risk factors including glucocorticoid use and genetic predispositions can be a critical confounding factors when evaluating the effects of alcohol on the development of ONFH.[52, 53] However, it is difficult to evaluate the additive effects of other risk factors. The ARCO criteria have excluded patients who have other risk factor(s) other than excessive alcohol intake from AA-ONFH and exclusion criteria included a history of trauma, moderate- to high-dose glucocorticoid therapy, hereditary coagulopathies, Caisson disease, radiation therapy involving the femoral head, non-glucocorticoid chemotherapeutics for

cancer, sickle cell disease or Gaucher's disease.

The current Delphi survey defined the classification criteria of AA-ONFH so that clinicians and researchers can objectively classify these patients. However, as described in the part I study of GA-ONFH, the Delphi consensus method has limited validity in terms of scientific evidence and the iteration characteristics of the Delphi technique can potentially enable investigators to mold opinions. Also, because the classification criteria are not synonymous with diagnostic criteria, ARCO does recommend that the criteria should not be used as diagnostic criteria for AA-ONFH in clinical practice or as guidance in handling a legal issue. For research purposes, this classification criteria aims to have a high specificity (i.e., low false positivity) at the expense of a reduction of in sensitivity (i.e. increase in false negative results). The current classification criteria were established via expert consensus rather than quantitative analysis using patient data set. Therefore, the validity and reliability should be evaluated in a further study with large sample size. Through these ARCO classification criteria for AA-ONFH, more research data will be accumulated and our understanding will be increased. It is hoped that this work will be the impetus for the further development of diagnostic and treatment methods for this disease.

Conclusion

The current Delphi survey provides classification criteria for AA-ONFH. ARCO recommends using these criteria for studies about ONFH.

Disclosure statement The authors declare no conflict of interest.

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Supplementary Information Legend

Supplementary material 1. The six key studies were selected from 50 studies relevant to GA-ONFH by the review of task force team.